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Polymorphisms in DNA repair genes and risk of non-Hodgkin lymphoma among women in Connecticut

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Abstract Several hereditary syndromes characterized by defective DNA repair are associated with high risk of non-Hodgkin lymphoma (NHL). To explore whether common polymorphisms in DNA repair genes affect risk of NHL in the general population, we evaluated the association between single nucleotide polymorphisms (SNPs) in DNA repair genes and risk of NHL in a population-based case–control study among women in Connecticut. A total of 518 NHL cases and 597 controls recruited into the study provided a biologic sample. Thirty-two SNPs in 18 genes involved in several DNA repair pathways were genotyped. Genotype data were analyzed by unconditional logistic regression adjusting for age and race. SNPs in four genes (*ERCC5, ERCC2, WRN*, and *BRCA1*) were associated with altered risk of NHL and diffuse large B-cell lymphoma (DLBCL), the major B cell subtype. In particular, *ERCC5* Asp1104His was associated with increased risk of NHL overall (OR: 1.46; 95% CI: 1.13–1.88; $P = 0.004$), DLBCL (OR: 1.44; 95% CI: 0.99–2.09; $P = 0.058$), and also T cell lymphoma. *WRN* Cys1367Arg was associated with decreased risk of NHL overall (OR: 0.71; 95% CI: 0.56–0.91; $P = 0.007$) and DLBCL (OR: 0.66; 95% CI: 0.45–0.95; $P = 0.024$), as well as follicular and marginal zone lymphomas. Genetic polymorphisms in DNA repair genes, particularly *ERCC5* and *WRN*, may play a role in the pathogenesis of NHL, especially for DLBCL. Further work is needed to extend these findings by carrying out extended haplotype analyses of these and related genes and to replicate the observations in other studies.

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Introduction

There has been a steady increase in the occurrence of non-Hodgkin lymphoma (NHL) in the past 50 years. The rising trend has been observed in all geographical regions covered by cancer registration, and is not restricted to any particular age or sex subgroups, or to predominantly urban or suburban areas (Hartge and Wang 2004). The impact of AIDS epidemic on lymphoma rates or improved diagnostic practices cannot fully explain the increase. Family history of cancer, medical conditions with decreased immune function, and viral infection (HTLV-1, EBV, hepatitis C) have been connected with NHL (Hartge and Wang 2004). Occupational and environmental exposure to some chemicals, dietary patterns, and reproductive factors may play a role but results have been inconsistent (Hartge and Wang 2004). In addition to exogenous exposures, individual genetic susceptibility may be important in the pathogenesis of NHL ((Hartge and Wang 2004). Although this

would not explain the rising incidence of NHL per se, genetic variants could interact with environmental exposures and thereby contribute to lymphomagenesis.

Several hereditary syndromes, including Ataxia telangiectasia (OMIM 208900), Bloom syndrome (OMIM 210900), and Nijmegan breakage syndrome (OMIM 251260), are characterized by defective DNA repair and high occurrence of lymphoma, indicating the important role of DNA repair in the pathogenesis and development of NHL. Chromosome aberrations are a hallmark of lymphoma and each type of lymphoma has one or more particular types of chromosome aberrations, e.g., the t(3,22) translocation in diffuse large B-cell lymphoma (DLBCL) and the t(14,18) translocation in follicular lymphoma (FL) (Chaganti et al. 2000). DNA repair mechanisms are important in maintaining genomic stability and defects in DNA repair can cause increased chromosomal aberrations (Griffin et al. 2005; Palitti 2004). Polymorphisms in DNA repair genes may modify repair capacity and alter risk of NHL. Here, we report associations between one or more SNPs and related haplotypes in 18 DNA repair genes (*ERCC5*, *ERCC2*, *ERCC1*, *RAD23B*, *XPC*, *WRN*, *BRCA1*, *BRCA2*, *LIG4*, *NBS1*, *XRCC2*, *XRCC3*, *XRCC4*, *RAG1*, *XRCC1,* *ADPRT*, *APEX1*, and *MGMT*) and NHL risk in a population-based case–control study among women in Connecticut, USA.

Subjects and methods

Study population

Details of this population-based case–control study were described elsewhere (Morton et al. 2003). In brief, incident female NHL cases were identified using the Yale Comprehensive Cancer Center's Rapid Case Ascertainment Shared Resource, a component of the Connecticut Tumor Registry. Eligible cases included female residents of Connecticut diagnosed with NHL (ICD-O, M-9590–9642, 9690–9701, 9740–9750), who were between the ages of 21 and 84 at the time of diagnosis, had no previous diagnosis of cancer (except non-melanoma skin cancer), and were alive at the time of the interview. From 1995 to 2001, 601 NHL eligible cases (72% of all eligible cases) agreed to participate in this study. All NHL cases were histologically confirmed according to both the Working Formulation and World Health Organization classification schemes (Herrinton 1998).

A population-based control group was enrolled in Connecticut using random digit dialing (RDD) for women younger than 65 years or using randomly the files of the Centers for Medicare and Medicaid Services (CMMS) for women 65 years of age and older. The participation rate was 69% for RDD controls and 47% for CMMS controls. The controls were frequency matched to cases by age within 5-year groups. A total of 717 qualified controls completed in-person interview. This study was conducted, based on a protocol approved by the Human Investigations Committee at Yale University and the Connecticut Department of Health, and an Institutional Review Board of the National Cancer Institute.

Of the 601 cases and 717 controls, biological samples (blood or buccal cells) were available from 518 cases and 597 controls. Demographic features of these subjects with biologic samples are comparable to those without biologic samples (data not shown). Among them, there were 411 B-cell lymphomas, which include 161 DLBCLs, 119 FLs, 59 small cell lymphocytic lymphomas/chronic lymphocyticleukemias (SLL/CLL), 35 marginal zone lymphomas (MBL), and 39 T-cell lymphomas.

Genotyping

DNA was extracted from 996 blood samples (461 cases and 535 controls) and 119 buccal cell samples (57 cases and 62 controls) using phenol–chloroform extraction (Garcia-Closas et al. 2001) and genotyped by TaqMan-based real-time PCR on an ABI 7900HT sequence detection system at the Core Genotyping Facility of NCI as described on the SNP500 website (http://www.snp500cancer.nci.nih.gov) (Packer et al. 2004). SNPs were selected for study based on a minimum allele frequency of 0.05, and evidence of association in previous epidemiology studies, evidence of function, or to extend genomic coverage for a given gene. More than 95% of the blood cell samples were successfully genotyped for all SNPs except *WRN* [rs2725362] (93%). However, due to limited DNA extracted from buccal cells, only 14 out of 32 SNPs were determined successfully for subjects with buccal cell samples, in which 22–40% samples were genotyped for 11 SNPs (*BRCA1* [rs16941], *BRCA2* [rs144848], *ERCC5* [rs17655], *MGMT* [rs2308321 and rs12917], *NBS1* [rs1805794], *RAD23B* [rs1805329], *XRCC1* [rs25487, rs25489, and rs1799782], and *RAG1* [rs2227973]) and 67–81% samples for 3 SNPs (*APEX1* [rs3136820], *LIG4* [rs1805388], and *WRN* [rs1346044]). Quality control samples for all SNPs were re-checked and concordance rates were above 98% for each (100% for *WRN* Val114Ile and *XRCC1* Arg280His, and 98% for *BRCA1* Glu997Gly).

Statistical analysis

Tests for departure from Hardy–Weinberg equilibrium was tested for each SNP with a Pearson χ^2 or an exact test if any of the cell counts were < 5. Measure of pairwise linkage disequilibrium (LD) and the test for LD at one gene were carried out using the program HaploView (http://www.broad.mit.edu/personal/jcbarret/haploview/). Genotype data were analyzed with the homozygotes of the common allele as the reference group. Unconditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals

(CI) for the association between each SNP and NHL risk, adjusting for age and race. Test for linear trend was conducted by including genotype as a continuous variable in the logistic regression model. Data were analyzed, stratified by histology, in which all controls were used.

P-values were adjusted by the false discovery rate (FDR) method developed by Benjamini and Hochberg (1995) to take into account multiple tests performed in their study. In addition, a two-stage omnibus test was applied to evaluate the global impact on NHL risk of genetic polymorphisms in DNA repair genes evaluated in this study, controlling for both intra-genetic family-wise error rate and the FDR (Rosenberg et al. 2005).

Haplotype block structure was examined for SNPs within the same gene using the four gamete rule (Wang et al. 2002). Individual haplotypes were estimated for SNPs within the same haplotype block using the expectation maximization (EM) algorithms, and overall differences in the frequency distribution of haplotypes between cases and controls were tested using the permutation omnibus test available in SAS/Genetics. The effects of individual haplotypes were estimated using the best haplotype pairs in an unconditional logistic regression model with the most common haplotype as the reference. Data were analyzed with the Statistical Analysis Software 8.02 (SAS Institute Inc. 1996), if not otherwise specified.

Results

Selected demographic characteristics of cases and controls are shown in Table 1. Cases and controls were similar with respect to age, race, and reported family history of cancer. In total, 32 SNPs in 18 genes involved in different DNA repair pathways were genotypes, including non-synonymous mutations and synonymous substitutions in coding regions, as well as SNPs in non-coding regions (Table 2).

Table 1 Characteristics of study participants (n = 1,115) who provided blood or buccal cell samples for genotyping

Characteristic	Cases (%) (n = 518)	Controls (%) (n = 597)	P[a]
Age (years)			
< 40	43 (8.3%)	51 (8.5%)	0.60
40–49	59 (11.4%)	66 (11.1%)	
50–59	109 (21.0%)	109 (18.3%)	
60–69	132 (25.5%)	144 (24.1%)	
70+	175 (33.8%)	227 (38.0%)	
Race			
Caucasian	497 (95.9%)	561 (94.0%)	0.14
African-American	16 (3.1%)	17 (2.8%)	
Others	5 (1.0%)	19 (3.2%)	
Family history[b]			
No	110 (21.2%)	147 (24.6%)	0.06[c]
NHL	9 (1.7%)	3 (0.5%)	
Other cancers	399 (77.0%)	447 (74.9%)	
DNA source			
Blood	461 (89.0%)	535 (89.6%)	0.74
Buccal cells	57 (11.0%)	62 (10.4%)	

[a]Pearson χ^2 test
[b]Family history of cancer in first degree relatives
[c]Fisher's exact test

The distribution of all genotypes in controls was consistent with Hardy–Weinberg equilibrium in non-Hispanic Caucasians with the exception of *WRN* Val114Ile (P = 0.01), *BRCA1* Glu997Gly (P = 0.01), and *XRCC1* Arg280His (P = 0.01), for all of which the number of heterozygotes are decreased compared to the expected distribution. Genotype frequencies for cases and controls, and main effects of SNPs that showed significant associations for all NHL, B cell and/or T cell lymphomas are shown in Table 3, and results for B cell NHL subtypes are shown in Table 4. Results of non-significant SNPs are presented in Table 5.

Evaluation of the global impact on risk of NHL by an omnibus test for all DNA repair polymorphisms evaluated in this study provided evidence that variation in DNA repair genes may contribute to the pathogenesis of NHL (P = 0.07). More specifically, we found that polymorphisms in two genes in nucleotide excision repair (NER) were associated with risk of NHL. The *ERCC5* 1104His variant was associated with an increased risk of NHL overall (OR: 1.46; 95% CI: 1.13–1.88; P = 0.004), which was significant for B-cell lymphoma, DLBCL and T-cell NHL as well. The *ERCC2* 751Gln allele was inversely associated with all NHL (OR: 0.79; 95%CI: 0.61–1.02; P = 0.07) and DLBCL.

Among genes involved in the double strand break repair (DSBR) pathway, polymorphisms in *WRN*, *BRCA1*, *BRCA2*, and *XRCC3* were associated with altered risk of NHL or NHL subtypes. The *WRN* 1367Arg allele was significantly associated with a reduced risk of NHL (OR: 0.71; 95% CI: 0.56–0.91; P = 0.007) and for the major B cell subtypes: DLBCL and FL (Table 4). The *BRCA1* Glu997Gly variant was associated with a reduced risk of NHL (OR: 0.79; 95% CI: 0.62–1.02; P = 0.066), which was significant for DLBCL (Table 4), and the results remain significant if using expected distribution of the genotype among controls in non-Hispanic Caucasians only except that the P values for homozygous variant carriers became non-significant. In addition, the *BRCA2* Asn289His polymorphism was associated with a fourfold risk of T-cell NHL, whereas the *XRCC3* 241Met allele was associated with an increased risk of FL and MZBL.

In *XRCC1*, a gene that plays a role in base excision repair (BER), the 194Trp variant was significantly associated with a 50% reduced risk of FL, while the 280His allele was associated with an increased risk of T-cell NHL and SLL/CLL. For all those associations examined with NHL, the smallest P values adjusted for FDR were obtained from *ERCC5* 1104His (P_{FDR} = 0.11) and *WRN* 1367Arg (P_{FDR} = 0.11). We also analyzed the data among non-Hispanic Caucasians (96% of cases and 94% of controls) only and obtained

Table 2 Genes and single nucleotide polymorphisms analyzed in the study

Gene symbol	Location	SNP
Nucleotide excision repair		
ERCC5	13q22	Ex15 − 344 G > C (rs17655) Asp1104His
ERCC2	19q13.3	Ex10 − 16 G > A (rs1799793) Asp312Asn, Ex23 + 61 A > C (rs1052559) Lys751Gln
ERCC1	19q13.2-q13.3	IVS5 + 33 C > A (rs3212961)
RAD23B	9q31.2	Ex7 + 65 C > T (rs1805329) Ala249Val
XPC	3p25	Ex16 + 211 A > C (rs2228001) Lys939Gln
Double strand break repair		
WRN	8p12-p11.2	Ex4 − 16 G > A (rs4987236) Val114Ile, Ex9 − 109 G > A (rs1800391) Met387Ile, Ex34 − 93 T > C (rs1346044) Cys1367Arg
BRCA1	17q21	Ex12 + 1641 T > C (rs16940) Leu730Leu, Ex12 − 1485 C > T (rs799917) Pro830Leu, Ex12 − 984 A > G (rs16941) Glu997Gly, Ex12 − 549 A > G (rs16942) Lys1142Arg
BRCA2	13q12.3	Ex10 + 72 A > C (rs766173) Asn289His, Ex10 + 321 A > C (rs144848) Asn372His, Ex11 + 1487 A > G (rs1801406) Lys1132Lys, Ex11 + 1898 T > C (rs543304) Val1269Val
LIG4	13q33-q34	Ex2 + 54 C > T (rs1805388) Ile9Thr
NBS1	8q21-q24	Ex5 − 32 G > C (rs1805794) Glu185Gln
XRCC2	7q36.1	Ex3 + 442 G > A (rs3218536) Arg188His
XRCC3	14q32.3	Ex8 − 53 C > T (rs861539) Thr241Met
XRCC4	5q13-q14	IVS7 − 1 G > A (rs1805377), Ex8 + 34 T > G (rs1056503) Ser307Ser
RAG1	11p13	Ex2 + 2473 A > G (rs2227973) Lys820Arg
Base excision repair		
XRCC1	19q13.2	Ex6 − 22 C > T (rs1799782) Arg194Trp, Ex9 + 16 G > A (rs25489) Arg280His, Ex10 − 4 G > A (rs25487) Arg399Gln
PARP1	1q41-q42	Ex17 + 8 T > C (rs1136410) Val762Ala
APEX1	14q11.2-q12	Ex5 + 5 G > T (rs3136820) Asp148Glu
Direct reversal of damage		
MGMT	10q26	Ex2 − 25 C > T (rs12917) Leu84Phe, Ex4 + 3 A > G (rs2308321) Ile143Val, Ex4 + 119 A > G (rs2308327) Lys178Arg

very similar findings, so we report here only results using all subjects adjusting for race.

We examined pairwise LD between the SNPs and the haplotype block structure for genes in which more than one SNP was genotyped (i.e., *WRN*, *BRCA1*, *BRCA2*, *XRCC4*, *XRCC1*, and *MGMT*). Overall, haplotype analysis of these genes did not provide any additional information beyond that obtained by single SNP analyses. However, a haplotype in *BRCA1* (26% in cases vs. 31% in controls) with substitutions simultaneously at all four loci (Ex12 +1641 T > C—Ex12 − 1485 C > T—Ex12 − 984 A > G—Ex12 − 549 A > G) was associated with a reduced risk of NHL (OR: 0.82; 95% CI: 0.67–0.99; *P* value: 0.04) compared to the referent haplotype (68% in cases vs. 64% in controls).

Discussion

We studied 32 SNPs in 18 genes and found that *ERCC5* Asp1104His, *WRN* Cys1367Arg, *ERCC2* Lys751Gln, and *BRCA1* Glu997Gly polymorphisms were significantly associated with altered risk of NHL and for DLBCL, the major NHL subtype. *ERCC5* Asp1104His and *WRN* Cys1367Arg are particularly notable in that they were associated with one or more additional histological subtypes and had the most statistically significant findings. These results support the hypothesis that genetic polymorphisms in DNA repair genes may modify the risk of NHL.

The NER pathway repairs bulky DNA adducts such as UV-light-induced photolesions, intrastrand cross-links, and large chemical adducts in the transcribed or the non-transcribed strands. *ERCC5* encodes a structure-specific endonuclease and also a 5′-3′ exonuclease, which is required for both transcription-coupled NER (TC-NER) and global genomic NER (Christmann et al. 2003). Expression of *ERCC5* was increased in mouse trigeminal ganglion latently infected with Herpes simplex virus type 1, in transforming growth factor α/c-myc double-transgenic mice and in a cisplatin-resistant cell line (Higaki et al. 2004; Hironaka et al. 2003; Sakamoto et al. 2001), and lowered expression of *ERCC5* was

Table 3 Logistic regression analysis for single nucleotide polymorphisms (SNPs) in selected DNA repair genes on the risk of non-Hodgkin lymphoma (NHL) among women in Connecticut

SNP	Controls	All NHL				B cell				T cell			
		Cases	OR[a]	95% CI	*P*	Cases	OR[a]	95% CI	*P*	Cases	OR[a]	95% CI	*P*
Nucleotide excision repair gene													
ERCC5													
Ex15 − 344 G > C (rs17655)													
Asp1104His													
GG	352	260	Ref.			214	Ref.			15	Ref.		
GC	169	170	1.42	1.08–1.86	0.011	130	1.33	0.99–1.77	0.055	16	2.24	1.07–4.68	0.033
CC	29	34	1.70	1.00–2.91	0.052	26	1.59	0.91–2.81	0.106	1			
CG + GG	198	204	1.46	1.13–1.88	0.004	156	1.36	1.04–1.79	0.027	17	2.04	0.98–4.23	0.056
Trend			1.36	1.10–1.67	0.004		1.29	1.04–1.61	0.022		1.47	0.83–2.61	0.185
ERCC2													
Ex23 +61 A > C (rs1052559)													
Lys751Gln													
AA	207	203	Ref.			163	Ref.			14	Ref.		
AC	256	189	0.74	0.57–0.98	0.033	155	0.76	0.57–1.02	0.068	13	0.73	0.33–1.59	0.424
CC	67	64	0.96	0.65–1.43	0.854	48	0.90	0.59–1.38	0.633	5	1.12	0.39–3.26	0.830
AC + CC	323	253	0.79	0.61–1.02	0.070	203	0.79	0.60–1.04	0.095	18	0.81	0.39–1.66	0.561
Trend			0.91	0.76–1.09	0.318		0.89	0.73–1.09	0.260		0.96	0.56–1.64	0.878
Double strand break repair gene													
WRN													
Ex34−93 T > C (rs1346044)													
Cys1367Arg													
TT	313	305	Ref.			249	Ref.			20	Ref.		
TC	238	161	0.70	0.55–0.91	0.007	122	0.65	0.49–0.86	0.002	15	1.04	0.52–2.09	0.910
CC	39	29	0.78	0.47–1.30	0.338	23	0.76	0.44–1.31	0.324	2			
TC + CC	277	190	0.71	0.56–0.91	0.007	145	0.67	0.51–0.87	0.002	17	1.02	0.52–2.00	0.954
Trend			0.79	0.65–0.96	0.019		0.75	0.61–0.93	0.009		0.99	0.57–1.72	0.977
BRCA1													
Ex12−984 A > G (rs16941)													
Glu997Gly													
AA	276	261	Ref.			209	Ref.			21	Ref.		
AG	212	166	0.84	0.64–1.09	0.190	134	0.84	0.63–1.12	0.234	11	0.70	0.33–1.49	0.356
GG	66	40	0.65	0.42–0.99	0.047	29	0.58	0.36–0.93	0.025	2			
AG + GG	278	206	0.79	0.62–1.02	0.066	163	0.78	0.60–1.02	0.067	13	0.64	0.31–1.30	0.215
Trend			0.82	0.68–0.98	0.032		0.79	0.65–0.97	0.023		0.67	0.38–1.18	0.170
BRCA2													
Ex10 + 72 A > C (rs766173)													
Asn289His													
AA	494	432	Ref.			349	Ref.			26	Ref.		
AC	33	22	0.76	0.44–1.34	0.345	14	0.60	0.31–1.14	0.115	7	4.22	1.69–10.57	0.002
CC	2	1				1							
AC + CC	35	23	0.75	0.43–1.29	0.300	15	0.60	0.32–1.12	0.107	7	3.97	1.60–9.90	0.003
Trend			0.76	0.45–1.26	0.282		0.63	0.35–1.13	0.119		3.15	1.36–7.28	0.007
Base excision repair gene													
XRCC1													
Ex9 + 16 G > A (rs25489)													
Arg280His													
GG	469	397	Ref.			319	Ref.			24	Ref.		
GA	48	48	1.19	0.78–1.82	0.416	34	1.04	0.65–1.66	0.861	8	3.30	1.40–7.78	0.006
AA	5	5	1.16	0.33–4.04	0.816	4	1.15	0.31–4.31	0.839	1			
GA + AA	53	53	1.19	0.79–1.79	0.403	38	1.05	0.68–1.64	0.821	9	3.36	1.48–7.65	0.004
Trend			1.16	0.81–1.65	0.428		1.05	0.71–1.55	0.799		2.66	1.35–5.26	0.005

[a]Adjusted for age and race

associated with smoking related cancers (Cheng et al. 2000; Cheng et al. 2002). It was found that *ERCC5* normally suppresses UV-induced apoptosis (Clement et al. 2006). This suggests that *ERCC5* possesses secondary functions beyond the nuclease activity, such as RNA polymerase I and II transcriptions, recruitment of XPF-ERCC1, and DNA binding (Sarker et al. 2005; Shiomi et al.2005). The C-terminus of *ERCC5* is particularly important for the non-catalytic activity in the transcription-coupled repair (TCR) of oxidative DNA damage (Shiomi et al. 2005). The Asp1104His polymorphism is located in the region. Even though the

Table 4 Logistic regression analysis for SNPs in selected DNA repair genes on the risk of B cell NHL subtypes among women in Connecticut

	Controls	DLBCL				Follicular				MZBL				SLL/CLL			
		Cases	OR[a]	CI	*P*	Cases	OR[a]	CI	*P*	Cases	OR[a]	CI	*P*	Cases	OR[a]	CI	*P*
Nucleotide excision repair gene																	
ERCC5																	
Ex15 − 344 G > C (rs17655)																	
Asp1104His																	
GG	352	84	Ref.			65	Ref.			16	Ref.			35	Ref.		
GC	169	52	1.36	0.92–2.03	0.126	36	1.25	0.79–1.96	0.340	14	1.93	0.91–4.06	0.085	14	0.84	0.43–1.61	0.591
CC	29	12	1.91	0.92–3.95	0.082	5	1.12	0.41–3.04	0.832	2				4	1.28	0.41–4.02	0.670
CG + GG	198	64	1.44	0.99–2.09	0.058	41	1.23	0.80–1.90	0.353	16	1.90	0.92–3.91	0.081	18	0.90	0.49–1.65	0.734
Trend			1.37	1.02–1.85	0.036		1.16	0.81–1.65	0.428		1.57	0.90–2.74	0.114		0.99	0.61–1.60	0.952
ERCC2																	
Ex23 + 61 A > C (rs1052559)																	
Lys751Gln																	
AA	207	74	Ref.			41	Ref.			8	Ref.			28	Ref.		
AC	256	58	0.64	0.43–0.95	0.026	46	0.90	0.57–1.43	0.650	17	1.73	0.73–4.09	0.214	21	0.59	0.33–1.07	0.085
CC	67	15	0.63	0.34–1.18	0.149	19	1.43	0.77–2.64	0.258	6	2.28	0.76–6.85	0.143	4	0.43	0.14–1.27	0.126
AC + CC	323	73	0.64	0.44–0.92	0.018	65	1.01	0.66–1.55	0.971	23	1.84	0.81–4.20	0.147	25	0.56	0.32–0.99	0.044
Trend			0.73	0.55–0.98	0.034		1.12	0.83–1.53	0.452		1.53	0.90–2.60	0.117		0.62	0.40–0.99	0.043
Double strand break repair gene																	
WRN																	
Ex34 − 93 T > C (rs1346044)																	
Cys1367Arg																	
TT	313	99	Ref.			73	Ref.			23	Ref.			34	Ref.		
TC	238	48	0.64	0.44–0.94	0.024	34	0.63	0.41–0.98	0.042	8	0.45	0.20–1.02	0.055	19	0.74	0.41–1.34	0.320
CC	39	9	0.75	0.35–1.60	0.452	4	0.45	0.15–1.30	0.140	2				6	1.49	0.58–3.80	0.406
TC + CC	277	57	0.66	0.45–0.95	0.024	38	0.61	0.40–0.93	0.021	10	0.48	0.22–1.03	0.058	25	0.84	0.49–1.45	0.538
Trend			0.74	0.54–1.00	0.050		0.65	0.45–0.93	0.019		0.59	0.31–1.13	0.109		0.99	0.64–1.53	0.967
BRCA1																	
Ex12 − 984 A > G (rs16941)																	
Glu997Gly																	
AA	276	87	Ref.			60	Ref.			16	Ref.			29	Ref.		
AG	212	48	0.73	0.49–1.08	0.114	38	0.85	0.54–1.33	0.472	13	1.03	0.48–2.19	0.940	23	1.03	0.58–1.84	0.919
GG	66	12	0.58	0.30–1.12	0.104	7	0.50	0.22–1.15	0.105	3	0.76	0.21–2.68	0.665	4	0.57	0.19–1.69	0.309
AG + GG	278	60	0.69	0.48–1.00	0.050	45	0.77	0.50–1.17	0.220	16	0.96	0.47–1.97	0.921	27	0.92	0.53–1.60	0.772
Trend			0.75	0.56–0.99	0.042		0.77	0.55–1.06	0.109		0.92	0.54–1.57	0.768		0.86	0.56–1.30	0.471
XRCC3																	
Ex8 − 53 C > T (rs861539)																	
Thr241Met																	
CC	216	65	Ref.			31	Ref.			6	Ref.			20	Ref.		
CT	229	63	0.94	0.63–1.41	0.779	50	1.53	0.94–2.50	0.088	19	3.00	1.17–7.68	0.022	28	1.27	0.69–2.32	0.444
TT	87	19	0.73	0.41–1.29	0.272	24	1.86	1.03–3.35	0.040	4	1.60	0.44–5.82	0.475	5	0.60	0.22–1.64	0.317
CT + TT	316	82	0.88	0.61–1.28	0.513	74	1.62	1.03–2.56	0.038	23	2.60	1.04–6.51	0.042	33	1.08	0.60–1.94	0.791
Trend			0.87	0.67–1.14	0.317		1.38	1.03–1.84	0.030		1.37	0.82–2.30	0.225		0.90	0.60–1.35	0.602
Base excision repair gene																	
XRCC1																	
Ex6 − 22 C > T (rs1799782)																	
Arg194Trp																	
CC	470	126	Ref.			100	Ref.			28	Ref.			48	Ref.		
CT	79	23	1.05	0.63–1.75	0.837	7	0.40	0.18–0.90	0.027	4	0.88	0.30–2.60	0.824	8	1.06	0.48–2.34	0.884
TT	4					1											
CT + TT	83	23	1.01	0.61–1.67	0.971	8	0.45	0.21–0.95	0.038	4	0.83	0.28–2.42	0.728	8	1.00	0.46–2.21	0.993
Trend			0.96	0.59–1.57	0.884		0.51	0.25–1.04	0.063		0.79	0.28–2.20	0.652		0.95	0.45–2.01	0.890
Ex9 + 16 G > A (rs25489)																	
Arg280His																	
GG	469	132	Ref.			91	Ref.			25	Ref.			45	Ref.		
GA	48	10	0.74	0.36–1.51	0.414	10	1.07	0.52–2.19	0.857	3	1.16	0.34–3.98	0.817	9	2.03	0.93–4.42	0.076
AA	5					1				1				2			
GA + AA	53	10	0.68	0.33–1.37	0.279	11	1.07	0.54–2.13	0.850	4	1.39	0.47–4.16	0.555	11	2.22	1.08–4.58	0.031
Trend			0.65	0.33–1.27	0.207		1.06	0.58–1.94	0.854		1.47	0.61–3.55	0.389		2.01	1.11–3.63	0.021

[a]Adjusted for age and race

Table 5 Logistic regression analysis for non-signiifcant SNPs of DNA repair genes on the risk of NHL among women in Connecticut

Genes and SNPs	Controls	Cases	OR[a]	95% CI	*P*
Nucleotide excision repair gene					
ERCC2					
Ex10 − 16 G > A (rs1799793) Asp312Asn					
GG	226	199	Ref.		
GA	238	189	0.88	0.67–1.15	0.34
AA	70	57	0.90	0.60–1.34	0.60
GA + AA	308	246	0.88	0.68–1.14	0.34
Trend			0.93	0.77–1.12	0.43
ERCC1					
IVS5 + 33 C > A (rs3212961)					
CC	386	332	Ref.		
CA	127	110	1.04	0.77–1.40	0.82
AA	11	7	0.82	0.31–2.19	0.69
CA + AA	138	117	1.02	0.76–1.37	0.89
Trend			1.00	0.77–1.30	1.00
RAD23B					
Ex7 + 65 C > T (rs1805329) Ala249Val					
CC	380	343	Ref.		
CT	153	121	0.88	0.66–1.16	0.36
TT	24	13	0.60	0.30–1.20	0.15
CT + TT	177	134	0.84	0.64–1.10	0.20
Trend			0.83	0.66–1.05	0.12
XPC					
Ex16 + 211 A > C (rs2228001) Lys939Gln					
AA	172	132	Ref.		
AC	268	238	1.15	0.86–1.53	0.36
CC	94	87	1.19	0.82–1.72	0.37
AC + CC	362	325	1.16	0.88–1.52	0.30
Trend			1.10	0.91–1.32	0.33
Double strand break repair gene					
WRN					
Ex4 − 16 G > A (rs4987236) Val114Ile					
GG	475	408	Ref.		
GA	49	44	1.05	0.68–1.62	0.82
AA	5	1			
GA + AA	54	45	0.97	0.64–1.48	0.90
Trend			0.91	0.62–1.34	0.64
Ex9 − 109 G > A (rs1800391) Met387Ile					
GG	442	372	Ref.		
GA	86	69	0.94	0.67–1.33	0.73
AA	1	2			
GA + AA	87	71	0.96	0.68–1.35	0.80
Trend			0.97	0.70–1.36	0.88
BRCA1					
Ex12 + 1641 T > C (rs16940) Leu730Leu					
TT	244	224	Ref.		
TC	210	180	0.94	0.72–1.24	0.67
CC	56	36	0.70	0.44–1.11	0.13
TC + CC	266	216	0.89	0.69–1.15	0.39
Trend			0.88	0.72–1.07	0.19
Ex12 − 1485 C > T (rs799917) Pro830Leu					
CC	230	215	Ref.		
CT	228	193	0.92	0.71–1.21	0.57
TT	74	51	0.70	0.46–1.08	0.11
CT + TT	302	244	0.88	0.68–1.13	0.31
Trend			0.87	0.72–1.05	0.14
Ex12 − 549 A > G (rs16942) Lys1142Arg					
AA	245	223	Ref.		
AG	226	189	0.93	0.71–1.22	0.61
GG	59	40	0.75	0.48–1.17	0.20
AG + GG	285	229	0.90	0.70–1.15	0.39
Trend			0.89	0.74–1.08	0.24
BRCA2					
Ex10 + 321 A > C (rs144848) Asn372His					
AA	301	250	Ref.		
AC	220	191	1.01	0.78–1.31	0.92
CC	34	35	1.19	0.72–1.97	0.50
AC + CC	254	226	1.04	0.81–1.33	0.77
Trend			1.05	0.86–1.28	0.61
Ex11 + 1487 A > G (rs1801406) Lys1132Lys					
AA	246	203	Ref.		
AG	229	202	1.07	0.82–1.40	0.63
GG	59	48	1.01	0.66–1.55	0.96
AG + GG	288	250	1.06	0.82–1.36	0.67
Trend			1.03	0.85–1.24	0.79
Ex11 + 1898 T > C (rs543304) Val1269Val					
TT	354	295	Ref.		
TC	161	147	1.10	0.84–1.45	0.48
CC	17	14	1.10	0.52–2.32	0.80
TC + CC	178	161	1.10	0.85–1.44	0.47
Trend			1.09	0.86–1.37	0.49
LIG4					
Ex2 + 54 C > T (rs1805388) Ile9Thr					
CC	431	366	Ref.		
CT	127	116	1.06	0.79–1.42	0.69
TT	17	10	0.67	0.30–1.49	0.33
CT + TT	144	126	1.01	0.77–1.34	0.92
Trend			0.97	0.76–1.24	0.81
NBS1					
Ex5 − 32 G > C (rs1805794) Glu185Gln					
GG	245	228	Ref.		
GC	260	199	0.82	0.63–1.06	0.14
CC	58	50	0.93	0.61–1.41	0.72
GC + CC	318	249	0.84	0.66–1.07	0.17
Trend			0.91	0.75–1.10	0.32
XRCC2					
Ex3 + 442 G > A (rs3218536) Arg188His					
GG	437	396	Ref.		
GA	89	61	0.73	0.51–1.04	0.08
AA	3	3			
GA + AA	92	64	0.74	0.52–1.05	0.09
Trend			0.77	0.55–1.07	0.12
XRCC3					
Ex8 − 53 C > T (rs861539) Thr241Met					
CC	216	171	Ref.		
CT	229	215	1.20	0.91–1.58	0.20
TT	87	70	1.00	0.69–1.45	1.00
CT + TT	316	285	1.14	0.88–1.48	0.32
Trend			1.04	0.87–1.24	0.69
XRCC4					
IVS7 − 1 G > A (rs1805377)					
GG	408	338	Ref.		
GA	109	98	1.11	0.81–1.52	0.52

Table 5 (Contd.)

Genes and SNPs	Controls	Cases	OR[a]	95% CI	*P*
AA	13	10	1.02	0.41–2.51	0.96
GA + AA	122	108	1.10	0.81–1.50	0.54
Trend			1.08	0.82–1.41	0.59
Ex8 + 34 T > G (rs1056503) Ser307Ser					
TT	408	346	Ref.		
TG	110	100	1.09	0.80–1.48	0.60
GG	13	11	1.10	0.45–2.64	0.84
TG + GG	123	111	1.09	0.80–1.47	0.59
Trend			1.07	0.82–1.40	0.60
RAG1					
Ex2 + 2473 A > G (rs2227973) Lys820Arg					
AA	429	350	Ref.		
AG	99	107	1.34	0.98–1.82	0.07
GG	14	8	0.79	0.32–1.94	0.60
AG + GG	113	115	1.28	0.95–1.72	0.11
Trend			1.18	0.90–1.53	0.23
Base excision repair					
XRCC1					
Ex6 − 22 C > T (rs1799782) Arg194Trp					
CC	470	414	Ref.		
CT	79	57	0.83	0.57–1.19	0.31
TT	4	1			
CT + TT	83	58	0.80	0.56–1.15	0.24
Trend			0.79	0.56–1.12	0.19
Ex10 − 4 G > A (rs25487) Arg399Gln					
GG	235	209	Ref.		
GA	226	202	1.01	0.77–1.32	0.96
AA	75	55	0.82	0.55–1.23	0.34
GA + AA	301	257	0.96	0.75–1.24	0.76
Trend			0.94	0.78–1.12	0.47
PARP1					
Ex17 + 8 T > C (rs1136410) Val762Ala					
TT	363	323	Ref.		
TC	160	125	0.89	0.67–1.18	0.43
CC	12	7	0.64	0.25–1.66	0.36
TC + CC	172	132	0.87	0.66–1.15	0.34
Trend			0.87	0.68–1.12	0.27
APEX1					
Ex5 + 5 G > T (rs3136820) Asp148Glu					
GG	226	184	Ref.		
GT	257	233	1.12	0.86–1.46	0.41
TT	102	80	0.95	0.67–1.35	0.78
GT + TT	359	313	1.07	0.83–1.37	0.60
Trend			1.00	0.84–1.19	0.99
Direct reversal of damage					
MGMT					
Ex2 − 25 C > T (rs12917) Leu84Phe					
CC	424	345	Ref.		
CT	124	121	1.18	0.88–1.58	0.26
TT	9	4	0.53	0.16–1.74	0.30
CT + TT	133	125	1.14	0.86–1.51	0.38
Trend			1.08	0.83–1.40	0.58
Ex4 + 13 A > G (rs2308321) Ile143Val					
AA	446	387	Ref.		
AG	104	79	0.87	0.63–1.20	0.38
GG	8	4	0.56	0.17–1.87	0.34
AG + GG	112	83	0.84	0.61–1.16	0.29
Trend			0.84	0.63–1.12	0.23
Ex4 + 119 A > G (rs2308327) Lys178Arg					
AA	427	374	Ref.		
AG	87	71	0.92	0.65–1.30	0.65
GG	9	6	0.72	0.25–2.06	0.54
AG + GG	96	77	0.90	0.65–1.26	0.55
Trend			0.90	0.67–1.21	0.48

[a]Adjusted for age and race

function of this polymorphism is uncertain, it is predicted to be a deleterious substitution by a sequence homology-based tool (Ng and Henikoff 2001), and has been reported to be associated with elevated risk of lung cancer (Jeon et al. 2003) and breast cancer (Kumar et al. 2003).

WRN is unique among the five human Recombinase Q (RecQ) members with an intrinsic 3′ to 5′ DNA helicase activity, a DNA-dependent ATPase characteristic, and a 3′ to 5′ exonuclease activity. It plays an important role in monitoring genome integrity and controlling the cell's response to genotoxic stress, and is involved in DSBR, BER, and mismatch repair (Ozgenc and Loeb 2005). Together with other related factors, *WRN* helps recruit the proper DNA repair factors to the site of the lesion. In addition, the *WRN* complex can direct the activation of the apoptotic pathway if the damage is excessive. Lack of *WRN* may result in deregulation of DNA damage monitoring and anomalous activation of DNA repair or apoptosis in response to specific types of DNA damage including oxidative DNA damage and DNA strand breaks (Karmakar and Bohr 2005). The expression of *WRN* has been connected to the expression of the Myc oncoprotein, which is implicated in the pathogenesis of lymphoma (Grandori et al.2004). We found a significant protective effect of the 1367Arg variant against NHL. The polymorphism is in close proximity to an important sequence (Lys1371-Arg1372-Arg1373) defined as the nuclear localization signal (Matsumoto et al. 1998). Even though the 1367Arg exhibits little change in activity relative to wild-type WRN in one type of in vitro assay (Kamath-Loeb et al. 2004), it has been found to play a protective role against a variety of age-related disorders (Castro et al. 2000; Ye et al. 1997).

In addition to *WRN*, SNPs in three other DSBR genes (*BRCA1*, *BRCA2*, and *XRCC3*) were associated with risk of NHL or specific subtypes. However, no data are available about the exact function of the *BRCA1* Glu997Gly and the *BRCA2* Asn289His polymorphisms. The gene product of *XRCC3* participates in homologous recombination. Both *XRCC3*−/− cells and homozygote individuals (Met/Met) exhibit significantly increased tetraploidy (Yoshihara et al. 2004), which is a common

feature and possibly an initial step of chromosome instability underlying lymphoma development (Atkin 2000). Increased levels of DNA damage level have been linked to the *XRCC3* Met allele (Araujo et al. 2002). Our result is consistent with these findings.

Our study has several strengths. It is a population-based study. Incident cases were histologically confirmed and information bias resulting from disease misclassification was minimized. The participation rates in cases and controls should not be associated with genetic polymorphism frequencies of these DNA repair genes (Bhatti et al. 2005). In addition, we found that SNPs in *ERCC5* and *WRN* showed consistent effects in the same direction among several NHL histologies (i.e, *ERCC5* Asp1104His and DLBCL, MZBL and T cell lymphomas; *WRN* Cys1367Arg and DLBLC, follicular and MZBL lymphomas). Nevertheless, in view of the low prior probability for many SNPs studied here, their uncertain function, the overall modest sample size and small sample size for most histologies, and *P* values that were not highly significant, it is likely that at least some of our findings are false positives (Wacholder et al. 2004).

In summary, we found that variants in genes that play an important role in several DNA repair pathways were associated with altered risk of NHL, especially for DLBCL. These findings suggest that common genetic polymorphisms in DNA repair genes may be important susceptibility factors for NHL but require replication in other studies. Identification of the key DNA repair pathways that play a role in lymphomagenesis may ultimately help to identify particular exposures or general classes of exposures that have contributed to the rise in NHL incidence over the past several decades. In addition, genetic variants in DNA repair may be relevant for predicting response to treatment and ultimately survival. To this end, we plan to carry out additional genotyping of tagged SNPs in key genes we report here to enable comprehensive evaluation of major genetic variants, and to analyze additional genes in the most promising pathways. Finally, pooled analyses and evaluation of gene-environment interactions across multiple studies should help to further clarify the role of variation in DNA repair and its impact on risk of NHL.

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